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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/042,488	03/16/1998	RONALD M. EVANS	SALK1520-2	5034

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EXAMINER
KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
1633	31

DATE MAILED: 12/20/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/042,488	Applicant(s) EVANS ET AL.	
	Examiner Sumesh Kaushal	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-13,15-24,39,40 and 47-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-13,15-24,39,40 and 47-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

The request filed on 05/14/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09042488 is acceptable and a CPA has been established. An action on the CPA follows.

Claims 10, 14, 25-38, 41-46 were canceled.

Claims 1, 6-7, 13, 20-24, 39-40 and 50-56 were amended.

Claims 57-77 were newly filed claims

Claims 1-9, 11-13, 15-24, 39-40 and 47-77 were pending and were examined in this office action.

Applicant's response filed on 08/08/01 has been fully considered but they are not persuasive, in view of the new ground(s) of rejection below as necessitated by the recent amendments.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 11-13, 15-24, 39-40 and 47-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, **had possession of the claimed invention**.

The invention as claimed encompass a method for modulating the expression of an exogenous gene in an isolated cell comprising a DNA construct comprising the exogenous gene is under the control of any and all response element(s), a modified ecdysone receptor which in the presence of a ligand and optionally in the further presence of a receptor capable of acting as any and all silent partner(s) binds to the response element. In addition, the scope of instant claims also encompass a method for modulating the expression of an exogenous gene in an isolated cell comprising a DNA construct comprising the exogenous gene is under the control of an ecdysone response element, any and all modified receptor(s) which in the presence of a ligand and optionally in the further presence of a receptor capable of acting as any and all silent partner(s) binds to the response element.

At best the specification as filed discloses modified ecdysone receptor GEcR (containing glucocorticoid response element) and VpEcR (containing Vp16 activation domain) from *Drosophila melanogaster* within the scope of genus comprising the claimed modified receptors (spec. page 6, line 19-33 and fig-1D). The specification further disclosed that Drosophila USP and it mammalian homolog RXR are the silent partner of insect Ecdysone receptor, which mediates ecdysone hormone responsiveness (spec. page 5, line 33 and fig-1A). In addition the specification disclosed a modified ecdysone receptor VgEcR contain mutation in 3 amino acid residues that render this modified receptor responsive to a hybrid responsive element E/GRE (ecdysone/glucocorticoid response element) see spec. page 6, line 19-33. In addition the specification teaches that the use of modified ecdysone receptor (VgEcR) in combination with hybrid responsive element E/GRE only enable the method as claimed wherein the response element has no binding affinity for FXR receptor (spec. Fig-1B).

However, there is no description any and all response elements and the respective ligands they respond to as encompassed by the invention now being claimed. Furthermore, the specification fails to disclose any and all modified receptors that mediates the transactivation of an exogenous gene operatively linked to any an all DNA-binding domains or any and all activation domains and has no binding affinity for FXR.

The state of the art at the time of filing was such that the ecdysone hormone responsiveness is mediated by the functional ecdysone response complex, a hetrodimer of the insect ecdysone receptor (EcR) either with its natural dimeric partner, the ultraspiracle gene product (USP) or with the retinoid X receptor (RXR) a mammalian homolog of USP (Hoppe et al Mol. Ther. 1(2):159-164, 2000). Similarly, the retinoic acid receptor and the thyroid hormone receptor require dimerization with a second nuclear receptor, the retinoid X receptor. The functional ecdysone receptor is composed of a hetrodimer between the ecdysone-binidng receptor (EcR) and a RXR homologue, the EcR/RXR complexes repress the transcription in the absence of ligand and recruit coactivators in the presence of the ligand in ecdysone receptor system (Ghbeish et al, PNAS98(7):3867-3872, 2001). However, no mammalian transcription factors have been shown to have a natural enhancer element like the EcRE, which is composed of two inverted half-sites of the sequence AGGTCA spaced by 1 nucleotide and it is difficult to preclude such a possibility (NO et al, PNAS 93:3346-3351, 1996, page 3349, col.1 para.2). The art at the time of filing further teaches that farnesoid X receptor (FXR) can activate certain synthetic promoters containing an EcRE response element in response to farnesoids. The modified ecdysone receptor VgEcR containing mutation in 3 amino acid residues render the modified receptor responsive to a hybrid responsive element called the E/GRE (ecdysone/glucocorticoid response element). Although FXR can activate a promoter containing the wild type EcRE, it cannot activate one containing the E/GRE. Similarly, the E/GRE linked reporter gene is not activated by GR nor does VgEcR activate a dexamethasone responsive promoter (NO et al, page 3349, col.1 para.2).

There is no description how the structure of Drosophila ecdysone receptor relates to the structure of any naturally occurring ecdysone receptors. In addition, the steroid/thyroid hormone superfamily receptors include members that would expected to have widely divergent functional properties. The specification fails to disclose any modified thyroid hormone receptor system wherein the response element has no binding affinity for FXR and the system modulates the expression of an exogenous gene as claimed.

The general knowledge in the art concerning ecdysone receptor does not provide any indication as how the structure of one receptor is representative of other unknown homologs having concordant or discordant functions. The specification only disclosed ecdysteroid induced responsiveness in a modified ecdysone receptor system comprising VpEcR (Drosophila) and E/GRE response element that has substantially no binding affinity for farnesoid-X-receptor. According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

Claims 1-9, 11-13, 15-24, 39-40 and 47-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modulating the expression of an exogenous gene in an isolated cell containing i) a DNA construct comprising the exogenous gene under the control of the disclosed modified ecydsone response element E/GRE wherein the response element has substantially no binding affinity for farnesoid-X-receptor (FXR), and ii) a modified ecdysone receptor (VgEcR) which in the presence of an exogenous ecdysteroid and in the presence of EcR silent partner (RXR) bind to the response element, does not reasonably provide enablement for the method as claimed wherein an isolated cell comprises a) any and all response elements that has substantially no binding affinity for FXR and b) any and all modified receptors and/or their silent partners containing any and all ligand binding domains, DNA binding domains and activation domains of any and all transcription factors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of instant claims encompass a method for modulating the expression of an exogenous gene in an isolated cell comprising a DNA construct comprising the exogenous gene is under the control of any and all response element(s), a modified ecdysone receptor which in

the presence of a ligand and optionally in the further presence of a receptor capable of acting as any and all silent partner(s) binds to the response element. The scope of instant claims also encompass a method for modulating the expression of an exogenous gene in an isolated cell comprising a DNA construct comprising the exogenous gene is under the control of an ecdysone response element, any and all modified receptor(s) which in the presence of a ligand and optionally in the further presence of a receptor capable of acting as any and all silent partner(s) binds to the response element. Furthermore, the scope of instant claims encompass the method as claimed wherein the exogenous gene is a therapeutic gene (see claims 19-21, 64-66). In addition, the scope of the method as claimed encompass the modulation of the expression of an exogenous gene in a mammalian subject (see claims 72-77).

The specification teaches modified ecydsone receptor GEcR (containing glucocorticoid response element) and VpEcR (containing Vp16 activation domain) obtained from *Drosophila melanogaster* within the scope of genus comprising the claimed modified receptors (spec. page 6, line 19-33 and fig-1D). The specification further disclosed that Drosophila USP and it mammalian homolog RXR are the silent partner of insect Ecdysone receptor, which mediates ecdysone hormone responsiveness (spec. page 5, line 33 and fig-1A). In addition the specification disclosed a modified ecdysone receptor VgEcR that contain mutation in 3 amino acid residues which render the modified receptor responsive to a hybrid responsive element E/GRE (ecdysone/glucocorticoid response element) see spec. page 6, line 19-33. In addition the specification teaches that the use of modified ecdysone receptor (VgEcR) in combination with hybrid responsive element E/GRE only enable the method as claimed, wherein the response element has no binding affinity for FXR receptor (Fig-1B).

The state of the art at the time of filing was such that the ecdysone hormone responsiveness is mediated by the functional ecdysone response complex, a hetrodimer of the insect ecdysone receptor (EcR) either with its natural dimeric partner, the ultraspiracle gene product (USP) or with the retinoid X receptor (RXR), a mammalian homolog of USP (Hoppe et al Mol. Ther. 1(2):159-164, 2000). Similarly, the retinoic acid receptor and the thyroid hormone receptor require dimerization with a second nuclear receptor, the retinoid X receptor. The

functional ecdysone receptor is composed of a hetrodimer between the ecdysone-binidng receptor (EcR) and a RXR homologue, the EcR/RXR complexes repress the transcription in the absence of ligand and recruit coactivators in the presence of the ligand in ecdysone receptor system (Ghbeish et al, PNAS98(7):3867-3872, 2001). However, no mammalian transcription factors have been shown to have a natural enhancer element like the EcRE, which is composed of two inverted half-sites of the sequence AGGTCA spaced by 1 nucleotide and it is difficult to preclude such a possibility (NO et al, PNAS 93:3346-3351, 1996, page 3349, col.1 para.2). The art at the time of filing teaches that farnesoid X receptor (FXR) can activate certain synthetic promoters containing an EcRE response element in response to farnesoids. The modified ecdysone receptor VgEcR containing mutation in 3 amino acid residues render the modified receptor responsive to a hybrid responsive element called the E/GRE (ecdysone/glucocorticoid response element). Although FXR can activate a promoter containing the wild type EcRE, it cannot activate one containing the E/GRE. Similarly, the E/GRE linked reporter gene is not activated by GR nor does VgEcR activate a dexamethasone responsive promoter (NO et al, page 3349, col.1 para.2).

The specification fails to teach any and all response elements and their respective ligands as encompassed by the invention as claimed. Furthermore, the specification fails to disclose any and all modified receptors that mediates the transactivation of an exogenous gene operatively linked to any an all DNA-binding domains or any and all activation domains and has no binding affinity for FXR. The specification fails to disclose any modified thyroid hormone receptor system wherein the response element has no binding affinity for FXR and the system modulates the expression of an exogenous gene as claimed. In addition, the specification fails to disclose the method for modulating the expression of an exogenous gene in isolated cells and/or a mammalian subject comprising a combination of any unrelated modified receptors their silent partners that modulates the expression of an exogenous gene operatively linked to any response element that has no binding affinity to the FXR.

Therefore it is unclear how one skill in the art would use the invention as claimed without excessive and undue amount of experimentation in view of the state of the art and the limited

guidance provided in the specification. To exercise the invention as claimed one would have to characterize and modify any and all receptor that regulates the expression of an exogenous gene operatively linked to any and all response elements containing any and all ligand binding domains, DNA-binding domains and activation domains. The experimentation required would include the identification and modification of thyroid hormone receptors herein the response element has no binding affinity for FXR and the system modulates the expression of an exogenous gene as claimed. In addition the experimentation required would further include the identification of the response elements that has no binding affinity for FXR receptor.

In addition, the invention as claimed encompass a method of modulating the expression of an exogenous gene in a mammalian subject (claims 72-77) and a method of modulating the expression of a therapeutic gene in an isolated cells (claims 19-21 and 64-66). Therefore the invention as claimed clearly falls in the realm of gene therapy. The Gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy. (Rosenberg et al, Science 287:1751, 2000, Verma, Mol. Ther. 1: 493, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997, Touchette, Nat. Med. 2(1) 7-8, 1996). None of the human studies to date has shown definite efficacy, despite more than 300 protocols involving 3000 patients since September 1990 (Anderson page 25 col.1 para.1). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. For example, in original clinical trial to treat adenosine deaminase (ADA) deficiency, patients received a total of 11 infusions of genetically modified autologous T-lymphocytes along with polyethylene glycol (PEG)-ADA. After 7 years of therapy no definitive conclusion is drawn as to the contribution of gene therapy to the present state of health of patients (Touchette, page 7 col.3, para.1; Anderson page 29 col.1, para.6). Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success (Touchette page 7, col.1 para. 2; page 8, col.2 para 1-4). The advisory panel further emphasized the need for

a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease. (Touchette, page 7, col.3, para.3).

Furthermore, it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors (Verma et al, see page 239 col.3 par.2, page 242, table-2). Although the retroviral vectors are the vectors of choice, they require target cells to be in cycling state for the successful delivery of gene of interest. On the other hand vector comprising DNA viruses and liposome coated DNA have been used to transduce non dividing cells but this results in a transient expression due to non-integration of transgenes in host cells (Verma et al page 242, table-2). In addition, the use of adenoviral and adeno associated viral vector is also problematic because these vectors elicits considerable immune response in vivo, which affects the sustained expression of the transduced genes (Verma et al, page 241, col.1, par.3; col.3, par.1). Furthermore, in vitro gene transfer studies are not predictive of in vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in vivo environment. In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacle to overcome. The viral particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets (Anderson WF, page 25 col.2, para.4).

The instant invention as claimed requires the delivery of the ecdysone responsive receptor complex into a mammalian subject via viral and non-viral methods, wherein the expression of a therapeutic gene is modulated by the administration of a formulation carrying an ecydsteroid and an activator for the silent partner of the receptor complex. The claimed ecdysone inducible system comprises **RXR and EcR** which hetrodimerize and transactivate the ecdysone response element capable of driving the expression of a gene of interest (specification Fig-2). It is not clear how both RXR and EcR constructs are delivered into a single cell in a mammalian subject. The specification fails to provide any guidance to selectively target both constructs into

a single cell in order to achieve ecdysteroid induced responsiveness in vivo. At best the specification teaches ecdysone responsiveness in a cell line (293) **in vitro** via transient transfection of a modified ecdysone receptor VgEcR, a hetrodimeric partner (RXR) and an ecdysone inducible reporter gene (example-3) which does not represent the modulation of the expression of an exogenous gene in a mammalian subject. Furthermore, the specification fails to provide any guidelines for determining which individual need to be administered with the formulation as claimed because an ecdysone inducible therapeutic gene should be in place in the host before the administration of any such formulation. Since, the presence of an ecdysone inducible system in a single cell in a mammalian subject is the prerequisite of instant invention, it is not clear how one skilled in the art would use the invention as claimed without any reasonable expectation of success.

Considering the unpredictability in the state of gene therapy art the specification as filed fails to disclose a single working example wherein expression of a wild type and/or therapeutic gene is modulated by transducing "an ecdysone inducible system" into a mammalian subject using a formulation comprising any and all types of ecdysteroids any activator for the silent partner of the receptor complex. Thus, in view of lack of specific guidance in the specification and considering the state of undeveloped art, the skilled artisan at the time of filing would be unable to use the claimed invention, without an excessive and undue amount of experimentation. The experimentation required would include the delivery of both RXR and EcR constructs into a single cell in a mammalian subject and subsequent modulation of the transduced ecdysone inducible system using the formulation comprising any and all naturally occurring ecdysones, ecdysone-analog and/or ecdysone mimics.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Christopherson et al, PNAS 89:6314-6318, 1992.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Deborah Clark can be reached on (703) 305-4051. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Tracey Johnson, whose telephone number is (703) 308-0377.

If the claims are amended canceled and/or added the applicants are required to follow Amendment Practice under 37 CFR § 1.121 *(http://www.uspto.gov)* and **A CLEAN COPY OF ALL PENDING CLAIMS IS REQUESTED** to facilitate further examination.

S. Kaushal, AU 1633

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER